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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/412,947	10/05/1999	SUDHIR AGRAWAL	HYZ-050CP2	1312

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ANN LOUISE KERNER PHD
HALE AND DORR LLP
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/29/2003 30

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/412,947	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Janet L Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 23-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *29* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

2. Claims 1-20 and 23-33 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting proliferation of cancer cells *in vitro*, and for inhibiting the proliferation of cancer cells *in vivo* and treating cancer in a subject comprising the administration of HYB 165, does not reasonably provide enablement for treatment of cancer in a patient *in vivo* comprising the administration of all synthetic modified oligonucleotides complementary to protein kinase A subunit RIα. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record in the Official Action mailed 10-24-2000, and those set forth below.

Applicant's arguments filed 11-07-2002 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification as filed teaches one of skill in the art how to make and use the invention. However, at the time of filing of the instant application, neither the prior art nor the specification as filed provided sufficient guidance to use a synthetic modified oligonucleotide, other than HYB 165, to treat cancer in an afflicted subject, wherein the sequence of the oligonucleotide is complementary to a portion of PKA subunit RIα other than the sequence to which HYB 165 is complementary. (It is noted that the oligonucleotide according to HYB 190 is complementary to the same portion of PKA RIα as HYB 165).

Applicants argue that the Examiner may be confusing the requirements under law for obtaining a patent with the requirement for obtaining government approval for marketing a particular drug for human consumption. Moreover, Applicants contend that "Determining effective parameters for the administration to cancer cells of a first agent comprising a synthetic, modified oligonucleotide....and determining the therapeutically effective amount required for the treatment would be considered a routine process by skilled artisans and would not require undue experimentation."

However, contrary to Applicant's assertions, in the assessment of the instant specification regarding enablement of the full scope of the claimed invention, the examiner has considered the following elements as per MPEP 2164.01 (a): (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill;(E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claimed invention comprises the use of synthetic, modified oligonucleotides complementary to all forms of, and all regions of PKA RIα, including all polymorphic and splice variants, and mutated forms of this mRNA, in combination with a second agent, to treat cancer in an afflicted subject.

However, all of the non-mismatched oligonucleotides disclosed in the specification as filed all comprise a sequence that would target the same region of PKA RIα mRNA molecule. There is no evidence that other hybrid, inverted hybrid, or inverted chimeric oligonucleotides targeting other regions of PKA RIα mRNA, including all polymorphic and variant forms of PKA

RIα mRNA would be effective for the *in vivo* treatment of cancer in an afflicted subject, nor has Applicants have not provided any guidance in this regard. Applicants have not provided any correlative evidence that the experimental results obtained by using chemically and structurally distinct compounds are generally predictive of the behavior of all antisense compounds, having a distinct sequence composition, length, chemical modification, and mRNA target. Applicants have not addressed this issue.

In regards to the state of the prior art and the level of predictability in the art, Branch (1998) teach "the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of nucleic acid therapeutics to their specified target *in vivo* is unpredictable, the internal structures of the targeted RNAs and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Moreover, there is clear evidence that the length, sequence, and modifications of an oligonucleotide influence its behavior in a cell. As stated in the previous Office Action, Crooke (1998) describes a variety of factors which influence cellular uptake and distribution of antisense base therapeutics, which include: length of the oligonucleotide, modifications, sequence of oligonucleotide and cell type. Due to the unpredictability in cellular behavior associated with variations in sequence, length, and modifications of the oligonucleotides encompassed by the present invention, it is likely that the examples comprising the use of the HYB 165 oligonucleotide are not representative of all oligonucleotides encompassed by the claimed invention. Applicants have not addressed the various factors that contribute to the unpredictable behavior of antisense compounds in different

cellular environments, as described by Crooke (1998). There is no clear nexus between the behavior of the oligonucleotide according to HYB 165 in cancer cells, and the behavior of all other synthetic modified oligonucleotides that target PKA RIα.

Moreover, Applicants have not addressed the issue regarding the phrase, "consists essentially of the nucleotide sequence set forth in SEQ ID NO:4," as set forth in claims 3, 14, and 25. Additionally, Applicants have not provided any guidance regarding the use of the full scope of compounds that "consists essentially of SEQ ID NO: 4." It is noted that the mismatched oligonucleotides set forth in Table 1, HYB 169, 168, and 188 of the specification as filed could be interpreted as, "consists essentially of SEQ ID NO:4," however these oligonucleotides overall were not effective to reduce tumor size in a mouse (See Figure 1).

Therefore, in view of the breadth of the claimed invention, and the lack of guidance in the specification as filed in regards to the use of oligonucleotides targeting a different region of a PKA RIα mRNA, and the high degree of unpredictability associated with the behavior of oligonucleotides in a cell as associated with the length, sequence, and modification of the oligonucleotide, the instant claims remain rejected under 35 USC 112, first paragraph since the specification as filed does not provide sufficient guidance and/or instruction that would allow one of skill in the art to practice the full scope of the claimed invention without undue experimentation. This conclusion is based upon the known unpredictability regarding the delivery and behavior of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, the lack of guidance provided in the specification as filed in this regard, and the breadth of the claimed invention.

Conclusion

3. THIS **ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
January 24, 2003

SEAN McGARRY
PRIMARY EXAMINER